F4 cont SUB F3

36. (amended) The synthetic oligonucleotide of claim 1 comprising the nucleotide sequence represented by SEQ ID NO: 45.

Please amend claim 50 as follows:

ES

50. (amended) A composition comprising at least one oligonucleotide of claim 1 and a pharmaceutically acceptable carrier.

Please cancel claim 225 without prejudice.

REMARKS

Summary #34-5 in Pkt JGL 5/22/01

As an initial matter, the undersigned would like to thank Examiner Larson for courtesies extended during an interview with Peter Corless conducted at the USPTO on August 21, 2000. The Examiner's helpful comments and suggestions are greatly appreciated.

The undersigned acknowledges that claims 17, 19 and 211 to 224 are free of the art of record. See paragraph 9 of the Office Action.

The claim amendments find support throughout the application including the Drawings and claims as filed originally.

For example, claim 1 has been rewritten to refer to particular SEQ ID NOS. Support for the amendment to claim 1 can be found, for example, in claim 225, now canceled, and in Table 1, page 16, etc.

Claims 8-20, 36, and 50 have been amended to improve claim language. In particular, the word "having" has been changed to "comprising".

No new matter has been added by virtue of the amendments.

At paragraph 2 of the Office Action, the disclosure was objected to because of alleged informalities. The objection has been addressed by this submission ie., the present amendment to page 29, line 2.

Applicants gratefully acknowledge withdrawal of the prior rejection of claims 1, 8-20, 36, 40-50 and 207-225 under 35 USC §112, first paragraph. See the Action at paragraph 3.

Claims 1, 40-46, and 50 stand rejected under 35 USC §102(e) as being anticipated by the Korba patent (US Pat. No. 5,646,262). While Applicants respectfully disagree with the rejection, grounds for it have been addressed by this submission.

In particular, the amendment to claim 1 addresses rejection ie., none of the SEQ ID NOS: 7-19 and 45 are taught by Korba as cited by the Examiner.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 1, 8-14, 36, 48, 49 and 225 stand rejected as being obvious over the Korba patent. See pages 4-5 of the Action. The rejection is respectfully traveresed.

The claimed invention features oligonucleotides from the 1829 to 1929 and 1872 to 1891 HBV regions. See Table 1 of the instant application eg., at pg. 16 (showing the positions of SEQ ID Nos. 7-19; and 45). On the other hand, Korba as cited, provides oligonucleotides directed to a smaller region of the HBV genome ie., 1841 to 1908. There is no specific or implied teaching in the cited patent that would provide any motivation to make and use the specific oligonucleotides featured in Applicants' claims.

In particular, many of Korba's oligonucleotides were reported to show little or no activity. See Korba's Table 1 is an example. It provides results of several antisense oligos that were unable to inhibit HBV virion DNA or HbcAg (HBV surface antigen).

See results for Korba's S6, S7, S9 and S10 in particular. See also Korba at col. 12, lines 43-50.

See also Figure 4 of Korba in which many oligonucleotides are reported to be incapable of inhibiting HBcAg.

In view of Korba's disclosure that many HBV targeted oligos did not work, at least in his hands, it is not seen how the cited patent can make it obvious to make and use oligos from the larger 1829 to 1929 HBV region. That is, it is not seen how Korba, as relied on, provides any express or implied teaching or motivation to make and use the particular oligos of SEQ ID Nos. 7-19 and 45. See amended claim 1. In contrast, Applicants have shown useful oligo activity as follows.

See Applicants' Table 3 at pg. 29 and page 30, first paragraph for example. Page 28, line 12 to page 29, line 6 provide details of an experiment in which claimed oligonucleotide 45 was used to inhibit replication of HBV in HBV-infected HepG2 cells. The level of inhibition of HBV replication was measured using southern hybridization. The results of this experiment, which show significant inhibition by oligonucleotide 45, are shown in Figure 11. The details of these experiments can be found in the Examples at pages 49-52. Thus, the claimed oligonucleotide SEQ ID NO: 45, for example, showed significant inhibition of HBV replication.

Additionally, claimed oligonucleotide SEQ ID NO: 18 was used in a viral inhibition assay in which the level of inhibition due to treatment with SEQ ID NO: 18 was determined by kinetic (or quantitative) PCR (at page 29, line 8 to page 30, line 3, and page 53, line 1 to page 54, line 18). In summary, HepG2 cells infected with HBV were treated with dilutions of antisense oligonucleotide SEQ ID NO: 18 or a control oligonucleotide. After treatment the cells were grown for 10 days and then supernatants from the cells were harvested. The amount of viral particles present in the supernatants of the treated versus control cells was determined by kinetic PCR using the primers SEQ ID NOS: 51 and 52. The results are shown in Table 3 page 29 of the specification. The IC_{50} value (or the concentration of antisense oligonucleotide

which produced 50% inhibition of viral replication) for SEQ ID NO: 18 was significantly lower (3.75-fold) as compared to the control oligonucleotide. Thus, the claimed oligonucleotide SEQ ID NO: 18 was used and showed significant inhibition of HBV replication.

Applicants respectfully disagree with the rejection as it pertains to the cited kit claims for reasons mentioned already.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 1, 8-15, 16, 18, 20, 36, 48, 49 and 225 stand rejected under the Korba patent as applied and further in view of Wu et al. (JBC 267, 12436, (1992) or Wu et al. (PCT application WO 93/04701). Applicants respectfully disagree.

As relied on, the Wu references are used to point out results of a single HBV anti-sense oligo. Some reduction in HBV surface antigen was reported. However, there is nothing in the cited Wu references taken individually or with Korba that provides any express or implied teaching to make and use the specific oligos featured in amended claim 1.

The unsuccessful oligos disclosed by Korba have been discussed above. Wu merely provides results for a single oligo in the face of Korba's many unsuccessful attempts to make active oligos. The Wu references, as relied on, do not remedy this defect and do nothing to support the instant rejection.

Accordingly, reconsideration and withdrawal of the rejection are requested.

On pages 7-8 of the Office Action, claims 1, 45 and 47 stand rejected as being obvious over the Korba patent in view of Uhlmann et al. (Chem. Rev. 90, (1990)). Applicants respectfully disagree.

As cited, Uhlman is used to show that a 2'-O-methyl modification helps to stabilize certain oligos. Korba is used by the Examiner to show that oligonucleotides can be linked by methyl phosphonate. However, there is no express or implied teaching in Uhlman taken by itself or with Korba that would provide any motivation to make and use such modified oligos. As discussed above, Korba reported that many oligos did not work in their hands. Uhlman, as cited, does not remedy this deficiency, and provides no express or implied teaching to make the specific oligos of amended claim 1 or dependent claims 45 and 47.

Accordingly, reconsideration and withdrawal of the rejection are requested.

Attached to this submission is a marked-up version of the changes made to the specification and claims. The attached page is captioned "version with markings to show changes made".

In view of the amendments and remarks made herein, it is respectfully submitted that the subject application is in a condition for immediate allowance, which action is earnestly requested.

If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**.

Respectfully submitted,

Date: March 19, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Section beginning at line 2 through line 6 of page 29 has been amended as follows:

of results than the other methods mentioned. When HBV6 (SEQ. ID NO: ~~32~~ 45) was titrated, significant inhibition was found (FIG. 11). Inhibition was also found to be mediated by the stem-loop bridging oligonucleotide, HBV67 (SEQ. ID NO: 37) (FIG. 12).

In the Claims:

Claim 1 has been amended as follows:

1. (amended) A synthetic oligonucleotide complementary to a portion of the HBV RNA secondary structure in the epsilon region of the HBV genome comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS: 7-19 and 45, which oligonucleotide inhibits HBV replication.

Claim 8 has been amended as follows:

8. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO:7.

Claim 9 has been amended as follows:

9. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 8.

Claim 10 has been amended as follows:

10. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 9.

Claim 11 has been amended as follows:

11. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 10.

Claim 12 has been amended as follows:

12. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 11.

Claim 13 has been amended as follows:

13. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 12.

Claim 14 has been amended as follows:

14. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 13.

Claim 15 has been amended as follows:

15. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 14.

Claim 16 has been amended as follows:

16. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 15.

Claim 17 has been amended as follows:

17. (amended) ~~A~~ The synthetic oligonucleotide of claim 1 ~~complementary to a portion of the HBV RNA and consisting of a nucleotide sequence set forth as~~ comprising the nucleotide sequence represented by SEQ ID NO: 16.

Claim 18 has been amended as follows:

18. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 17.

Claim 19 has been amended as follows:

19. (amended) ~~A~~ The synthetic oligonucleotide of claim 1 ~~complementary to a portion of the HBV RNA and consisting of a nucleotide sequence set forth as~~ comprising the nucleotide sequence represented by SEQ ID NO: 18.

Claim 20 has been amended as follows:

20. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 19.

Claim 36 has been amended as follows:

36. (amended) The synthetic oligonucleotide of claim 1 ~~having~~ comprising the nucleotide sequence represented by SEQ ID NO: 45.

Claim 50 has been amended as follows:

50. (amended) A ~~pharmaceutical~~ composition comprising at least one oligonucleotide of claim 1 and a pharmaceutically acceptable carrier.

Claim 225 has been cancelled without prejudice.

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